REMARKS

Claims 5 and 9-15 are rejected under 35 U.S.C. § 112, first paragraph. The rejection is addressed below.

Summary of Invention

The invention features *in vivo* methods of using XIAP antisense oligonucleotides to induce apoptosis. The methods involve administering to a subject diagnosed as having a proliferative disease nucleic acids complementary to a portion of human XIAP (SEQ ID NO:3).

Support for the Amendment

Support for the amendment of claims 5 and 8, which replaces the term "nucleic acid" with "oligonucleotide," is found at page 25, lines 3 and 4; at page 25, line 20, and at page 54, lines 10-21. Support for new claim 16, which recites a phosphorothioate modified oligonucleotide is found at page 56, lines 11 and 12. No new matter has been added.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 5, which features a method for inducing apoptosis in a cell in a mammal diagnosed as having a proliferative disease, and claims 9-15, which feature methods for treating a patient diagnosed as having a proliferative disease, stand rejected as lacking enablement based on the assertion that undue experimentation would be required to

practice the full scope of the invention. While the Examiner acknowledges that applicants have enabled the *in vivo* use of a particular antisense oligonucleotide (i.e., a 19-mer phosphorothioate modified antisense XIAP oligonucleotide), the Examiner argues that the use of an antisense oligonucleotide of any other length is unpredictable.

The proper test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). The M.P.E.P. § 2164.04 provides guidance regarding how this test is to be applied. The M.P.E.P. states:

> (I)t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain <u>why</u> it doubts the truth or accuracy of any statement in a supporting disclosure and *to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.* Otherwise there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure. (Emphasis added.)

In short, the Examiner must provide specific technical reasons showing why applicants' disclosure fails to satisfy the enablement requirement.

Evidence is required to support an enablement rejection

There is no reason to expect that a XIAP antisense oligonucleotide that is nineteen nucleotides in length is unique in its ability to induce apoptosis. In fact, applicants disclose that antisense XIAP oligonucleotides may be used to induce apoptosis in a cell *regardless of the length of the antisense oligonucleotide*. The Examiner has

acknowledged that applicants' disclosure enables the *in vivo* use of an antisense oligonucleotide of one particular length, and applicants' specification discloses that antisense molecules regardless of length are also expected to have the desired activity. At this juncture it is incumbent upon the Examiner to provide evidence showing why undue experimentation would be required to identify antisense oligonucleotides of other lengths that also induce apoptosis if this rejection is to be maintained.

Routine screening identifies antisense oligonucleotides

Contrary to the Examiner's assertion, the skilled artisan, provided with applicants' disclosure and using methods known in the art, could easily screen any antisense oligonucleotide, regardless of length, for its ability to induce apoptosis in a cell. As disclosed in applicants' specification, antisense oligonucleotides are designed using computer algorithms and screened *in vitro* to identify those that effectively inhibit protein expression (pages 54-55). Antisense oligonucleotides that are selected for efficacy *in vitro* are typically effective *in vivo*, as well, as stated in the Declaration of Dr. Eric Lacasse (the "Lacasse Declaration") ¶3. *In vivo* screening is used to identify those antisense oligonucleotides having the greatest efficacy (pages 55 and 56). Such screening is merely routine and thus cannot constitute undue experimentation.

Antisense oligonucleotide length is not a determinant of efficacy

Antisense oligonucleotides are potent and specific therapeutic molecules that share a common mechanism of action: they interfere with protein production by binding to a

complementary target mRNA. This binding inhibits protein production by interfering with the ribosome's ability to translate the mRNA, by interfering with splicing, and/or by inducing the degradation of the mRNA by RNAse H, an enzyme that recognizes and degrades mRNA/DNA hybrids. Regardless of the length of the antisense oligonucleotide, if it binds an accessible site on the target RNA in the cell, the antisense oligonucleotide will successfully inhibit protein production. (Lacasse Declaration ¶4)

As stated in the Lacasse Declaration ¶5, the results shown in Exhibits A (Shankar et al., J. of Neurochem. 79:426-436, 2001, hereafter "Shankar"), B (Kallio et al. FASEB J. express article, 10.1096/fj.01-0280fj3, 2001, hereafter "Kallio"), and C (Fukuda et al. Blood 100:2463-2471, 2002, hereafter "Fukuda"), previously of record, were carried out using methods available at the time applicants' priority document was filed. These references describe the use of antisense oligonucleotides of varying lengths to decrease the expression of an inhibitor of apoptosis protein, human survivin.

Shankar: 20-mer antisense oligonucleotide

Shankar describes the use of phosphorothioate modified antisense oligonucleotides, 20 nucleotides in length, to downregulate expression of human survivin expression and to induce apoptosis in neural tumor cells in culture. (Lacasse Declaration ¶6)

Kallio: 18-mer antisense oligonucleotide

Kallio describes the use of phosphorothioate modified antisense oligonucleotides, 18 nucleotides in length, to downregulate human survivin expression in HeLa and PtK1 cells in culture. The antisense oligonucleotides were conjugated to fluorescein

isothiocyanate, which allowed them to be visualized by fluorescence microscopy. (Lacasse Declaration ¶7)

Fukuda: full length antisense oligonucleotide

Fukuda describes the use of a full-length antisense survivin expression construct to modulate survivin expression in CD34 cells. (Lacasse Declaration ¶8)

As further evidence of enablement, the Lacasse Declaration provides U.S. Patent Nos. 5,958,771 ("the '771 patent") and 5,958,772 ("the '772 patent"), which were filed on December 3, 1998, and 6,087,173 ("the '173 patent"), which was filed on September 9, 1999 (Exhibits E, F, and G, respectively). As detailed below, each of these patents relates to the use of phosphorothioate modified antisense oligonucleotides to inhibit the expression of an IAP. This work was carried out using methods available at the time applicants' priority document was filed (Lacasse Declaration, ¶9).

The '771 patent describes the identification of twelve phosphorothioate modified 18-mer oligodeoxynucleotides that inhibited Cellular Inhibitor of Apoptosis-2 (cIAP-2) expression in cells *in vitro* (Table 1 and column 41, first paragraph) (Lacasse Declaration, ¶10).

The '772 patent describes the identification of six 18-mer phosphorothioate oligodeoxynucleotides that inhibited cIAP-1 expression in cells *in vitro* (Table 1 and column 39, first paragraph) (Lacasse Declaration, ¶11).

The '173 patent describes the identification of twenty-four 20-mer antisense oligodeoxynucleotides that inhibited XIAP expression in cells in vitro (Table 1, and column 41, first paragraph) (Lacasse Declaration, ¶12).

The examples cited above demonstrate that a full range of antisense oligonucleotide lengths work to inhibit the biological activity of an IAP target gene.

Clinical applications for antisense oligonucleotides

In addition, with respect to Exhibit D (Jansen et al., The Lancet Oncology 3:672-683, 2002; hereafter "Jansen"), previously of record, which provides a review of the *in vivo* use of antisense oligonucleotides of varying lengths, the Declaration of Dr. Lacasse states that the examples cited below, which relate to the use of phosphorothioate modified antisense oligonucleotides to inhibit protein production, were also carried out using methods available at the time applicants' priority document was filed. (Lacasse Declaration ¶13)

18-mer phosphorothioate antisense oligonucleotide

Jansen describes 1997 phase I clinical trials that used an 18-mer phosphorothioate Bcl-2 antisense oligonucleotide to treat patients diagnosed with non-Hodgkin lymphoma. Treatment with the 18-mer antisense oligonucleotide decreased BCL-2 protein levels in half of all patients that received it (page 676, right column, first paragraph). (Lacasse Declaration ¶14)

20-mer phosphorothioate antisense oligonucleotide

In a 1996 study by Yazaki et al. (Mol Pharmacol 50:236-42, 1996), which is also reviewed by Jansen, a 20-mer phosphorothioate modified antisense oligonucleotide was used to inhibit Protein Kinase C expression in glioblastoma xenografts in mice

(paragraph spanning page 677, right column, to page 678, left column). (Lacasse Declaration ¶15)

24-mer antisense oligonucleotide

A clinical pilot study, carried out by Ratjczak and colleagues in 1992, is also reviewed in Jansen. In this study, a 24-mer phosphorothioate modified antisense oligonucleotide was used *ex vivo* to successfully target and decrease the expression of the c-MYB proto-oncogene in bone-marrow cells harvested from patients with chronic myelogenous leukemia (page 679, right column, first paragraph). (Lacasse Declaration ¶16)

As further evidence of enablement, the Lacasse Declaration provides Exhibits H (Sugano et al., J. Biol. Chem. 271:19080-19083, 1996, hereafter "Sugano"), I (Galvin-Parton et al., J. Biol. Chem. 272: 4335-4341, 1997, hereafter "Galvin-Parton"), J (MacLeod et al., J. Biol. Chem. 270:8037-8043, 1995, hereafter "MacLeod"), and K (Ramchandani et al., P.N.A.S. 94:684-689, 1997, "Ramchandani"), all of which were received for publication prior to the date on which applicants' priority document was filed, and all of which relate to methods of using antisense oligonucleotides to inhibit protein production. (Lacasse Declaration ¶17)

21-mer antisense oligonucleotide

Sugano, published in 1996, used a 21-mer antisense oligonucleotide to inhibit expression of cholesteryl ester transfer protein (CETP), the enzyme that facilitates the transfer of cholesterylester from high density lipoprotein to apoB-containing lipoprotein. The asialoglycoprotein-coupled 21-mer antisense oligonucleotide, which was

administered to rabbits intravenously, decreased CETP biological activity and also decreased total cholesterol levels. (Lacasse Declaration ¶18)

39-mer antisense oligonucleotide

As published in February 1997, Galvin-Parton expressed a 39-mer antisense oligonucleotide in transgenic mice. This 39-mer antisense oligonucleotide, which targeted the nucleic acid encoding G-protein, $G\alpha_q$, decreased $G\alpha_q$ polypeptide levels, and caused an increase in body mass and hyperadiposity. (Lacasse Declaration ¶19)

600-mer and 20-mer antisense oligonucleotides

MacLeod, in 1995, expressed a 600-mer antisense oligonucleotide, which was complementary to DNA methyltransferase mRNA, in Y1 cells, a tumorigenic adrenocortical cell line. This antisense oligonucleotide decreased DNA methyltransferase gene expression, protein activity, and also decreased the ability of the Y1 cells to form tumors when injected into mice. (Lacasse Declaration ¶20)

In a related study published in January 1997, Ramchandani designed a phosphorothioate modified 20-mer antisense oligonucleotide that targeted the same region of DNA methyltransferase mRNA that was targeted by the 600-mer described by MacLeod. Ramchandani injected tumorigenic Y1 cells into the flanks of mice, allowed tumors to form, then administered the 20-mer antisense oligonucleotide to the tumor. The 20-mer and the 600-mer antisense oligonucleotides, though of widely differingly lengths, both decreased DNA methyltransferase levels and inhibited tumor growth. (Lacasse Declaration ¶21)

In sum, Shankar, Kallio, Fukuda, the '771 patent, the '772 patent, the '173 patent, Jansen, Sugano, Galvin-Parton, and MacLeod describe the use of antisense oligonucleotides that range in length between 18 and 600 nucleotides to inhibit the expression of a target gene and achieve a desired biological effect. These antisense oligonucleotides, regardless of length, bind to a complementary target mRNA and inhibit protein production, just as applicants' antisense oligonucleotides do. One skilled in the field of antisense, being familiar with the art available at the time of filing (of which the above is but a sample) would know that antisense molecules complementary to a portion of XIAP could be a variety of different lengths. (Lacasse Declaration ¶22)

The Examiner has acknowledged that applicants have enabled the *in vivo* use of a 19-mer antisense oligonucleotide to inhibit the biological activity of XIAP. No evidence has been made of record to show that a 19-mer antisense oligonucleotide is unique in its ability to inhibit XIAP biological activity. Indeed, applicants have provided abundant evidence showing that virtually any antisense oligonucleotide that binds to its complementary target mRNA will inhibit protein production. Thus, the enablement rejection should be withdrawn.

CONCLUSION

Applicants submit that this case is in condition for allowance, and such action is respectfully requested. If the Examiner does not concur, a telephonic interview with the undersigned is hereby requested.

Enclosed is a petition to extend the period for replying for three months from the date of receipt of applicants' Notice of Appeal on December 11, 2003, to and including June 14, 2004, which is a Monday. Applicants note that Friday, June 11, 2004, the date that was six months from the date on which the Office received applicants' Notice of Appeal, was a Federal holiday within the District of Columbia.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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